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How Are Children Different from Adults?

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Several factors alter an individual's risk for an environmentally related illness. A major determinant is the age of the individual. The toxicodynamic processes that determine exposure, absorption, metabolism, excretion, and tissue vulnerability are all age related. This paper discusses each of these processes and their variability with age, and illustrates these points with examples of environmentally related disease cases. — Environ Health Perspect 103(Suppl 6):7-12 (1995)

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Introduction

Several factors alter an individual's risk for an environmentally related illness. These include genetic background, nutrition, age, lifestyle, etc. These categories are not mutually exclusive but are influenced by each other. This article will focus on age as a susceptibility factor and specifically on how the toxicokinetic parameters of exposure, absorption, metabolism, distribution, and target organ susceptibility change during development (1).

Exposure

Exposure to an environmental agent is the first step in the sequence of environmentally related health effects. Exposures differ with developmental stage because the environments of children are different than those of adults.

When considering exposures, one must look at the exposures of an individual over the course of a day. In general it is true that people may move through several environments during a day, doing errands, going home, going to sleep. This is also true for infants and children, going to school, going to day care, going to play. What is needed is a sum total of all the exposures and some idea of the maximum exposure. But we are usually not able to put monitors on people and measure them. Usually, our estimates of exposure are from retrospective estimates. This is true not only for adults, but for children as well. Although

the total exposure in a day may be the same, the pattern of exposure may have totally different health effects. For example, nitrates in well water may cause methemoglobinemia. However, if they are ingested at a rate where the methemoglobin reductase can continue to keep the iron in hemoglobin in the reduced state, no health effect will occur. But if the dose exceeds the capacity of methemoglobin reductase, then methemoglobinemia will result (2). This is one mechanism that results in a threshold effect.

Exposures that have profound health effects on an individual may occur at periods of time that frequently are not considered, such as an exposure that may occur to the mother before the conception of that individual which may have a profound effect on that individual. For example, women who conceived after eating cooking oil contaminated with polychlorinated biphenyls (PCBs) gave birth to infants with yusho (3). The mechanism responsible is felt to be storage of PCBs in adipose tissue during exposure, which are then mobilized during pregnancy (4,5). Another example is that of a woman who was inadequately treated for plumbism in childhood and who gave birth to an infant with congenital lead poisoning (6). Storage of the lead in bone with mobilization during pregnancy is the most logical explanation for this result (7).

Another example of an exposure prior to conception, which may result in effects on the individual, is a preconception exposure that directly affects the ovum or sperm. The ovum, formed within the fetus of the future mother, is dependent on the exposures of both the grandmother and the mother. The ovum, therefore, is a stage of development that sums all the exposures of the other stages of development. Studies have measured xenobiotics in follicular

fluid, showing the potential for exposure (8). Sperm, in contrast, are created only a few hours to days prior to conception. Thus, the exposures to the sperm are dependent on paternal exposure in the periconception period.

In most instances, exposures to the fetus are dependent on the exposures to the mother. However, premature infants delivered after 24 weeks have very different exposures in the newborn intensive care unit (NICU), such as to noise, light, compressed gases, intravenous solutions, and benzyl alcohol (9). Not only is the NICU a unique environment, but these infants remain in the same environment often for months.

Exposures of newborns, infants, toddlers, school-age children, and adolescents can be discussed with reference to changes in physical location, breathing zones, oxygen consumption, food consumption, types of foods consumed, and normal behavioral development.

Physical Location

The physical location of children changes with development. The newborn is usually near the mother or held by the mother, so exposures will be like those experienced by the mother. The newborn frequently spends more time in a single environment for prolonged periods of time, i.e., a crib, rather than several different environments. Infants and toddlers are frequently placed on the floor or carpet, or on grass. Therefore, they have much more exposure to chemicals associated with these surfaces, such as formaldehyde and volatile organic chemicals from synthetic carpet (10) and pesticide residues from flea bombs (11).

Preambulatory children also may experience sustained exposure to noxious agents because they cannot remove themselves from their environment. An example is the

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infant who is badly sunburned due to the inability to protect himself/herself. It has been shown that the risk of skin cancer is most closely related to the amount of sun damage the skin sustains during the first 18 years of life (12).

School-age children spend a significant period of time at school, a very different physical environment than the house. Schools are frequently built on relatively undesirable land for economic reasons. These sites are frequently near highways (auto emissions and lead), under power lines (electromagnetic fields), or on old industrial sites (benzene, arsenic). Until relatively recently schools made frequent use of asbestos as a building material (13).

Adolescents not only have a new school environment, but begin to self-determine physical environments, often misjudging or ignoring the risks to themselves (14). In addition, many adolescents have part-time jobs that place them in physical environments which may be hazardous due to occupational exposures (15).

Breathing Zones

The breathing zone for an adult is typically 4 to 6 ft above the floor. However, for a child, it is closer to the floor and dependent on the height and mobility of the child. It is within these lower breathing zones that heavier chemicals such as mercury and large respirable particulates settle out (16) and radon accumulates (17). This is one factor that may have accounted for the case of acrodynia in Michigan from latex house paint (18).

Oxygen Consumption

Because of their larger surface-to-volume ratio, the metabolic rate of children is higher, and hence their oxygen consumption is greater. Therefore, their exposure to any air pollutant is greater. For example, if radon is present at 2 pCi/l, an adult with an average O_2 consumption rate of 3.5 ml/kg body weight/min will receive an exposure of 48 pCi/kg in 24 hr. In contrast, a 6-month-old child with an average O_2 consumption rate of 7 ml/kg body weight/min will receive an exposure of 96 pCi/kg in 24 hr, which is twice as much (19).

Quantity and Quality of Food Consumed

Just as O_2 requirement is higher for children as a function of their surface-to-volume ratio, so is caloric requirement. Not only do children maintain homeostasis, they also grow. Therefore, the amount of

food they consume per kilogram body weight is higher than that of the adult (20). Consider the amount of water consumed by an infant who receives formula reconstituted in boiled tap water. Average consumption is 6 oz/kg. (In comparison, for the average male adult, this is equivalent to drinking 35 cans of soda pop a day.) Blood lead levels greater than 10 $\mu\text{g/dl}$ have been found in infants with exposure to tap water in formula (6). It has also been shown that the types of food they consume differ from those of adults (21). The diets of many newborns are limited to breast milk. Breast milk has been documented to contain many environmental pollutants including lead, PCBs, and dioxins (22-24). Children's diets contain more milk products and more fruit and vegetables. When the level of exposure of children to Alar was calculated using a child's daily consumption of apples and apple products, an unacceptable level of risk for cancer was found (25).

Normal Behavioral Development

The normal behavioral development of a child will also influence his environmental exposures. A preambulatory infant will not be able to remove himself/herself from a noxious environment as mentioned earlier. Normal children pass through a developmental stage of intense oral exploratory behavior. Most objects grasped will be placed in the mouth. This behavior is one common etiology of lead poisoning in environments with high levels of lead dust (26). It also places the child at risk in environments that have not taken the oral orientation of children into account. One example is arsenic- and creosote-treated wood in playgrounds. Children will frequently place their mouths on these materials in the course of normal play (27). The ability to walk often places the child in unusual situations for play, such as used drums, mud puddles, or empty lots, environments where adults spend little time and which have the potential for dangerous exposures. As children become adolescents, they gain more and more freedom from parental authority. However, they are at a stage of development in which physical strength and stamina are at a peak, yet they are continuing to acquire abstract thinking (28). Therefore, they do not consider cause and effect, particularly delayed effects, in the same way adults do. They often place themselves in situations with greater risk due to this lack of per-

ception. An example is the increased incidence of farm injuries involving adolescents as compared to adults (29).

Absorption

Absorption generally occurs by four major pathways: transplacental, percutaneous, respiratory tract, and gastrointestinal tract. Each of these portals of entry is dependent on the developmental stage of the child.

Transplacental

During the fetal stage, a major pathway of absorption is the placenta. Until the late 1950s, the placenta was thought to protect the fetus from any maternal exposure. However, the experience with thalidomide drastically changed this paradigm (30). It is now known that several classes of compounds readily cross the placenta. Compounds of low molecular weight cross the placenta readily. Carbon monoxide is a good example of this type of chemical. Because carbon monoxide has a higher affinity for fetal compared to adult hemoglobin, the concentration of carboxyhemoglobin is higher in the fetus than in the mother (31). Lipophilic compounds such as polycyclic aromatic hydrocarbons and ethanol also readily gain access to the fetal circulation. PCBs have been measured in equal concentration in fetal and maternal blood (32). Fetal and maternal blood levels of ethanol are equal in pregnant ewes (33). The fetal liver does not express alcohol dehydrogenase until near term (34). Therefore, the majority of ethanol diffuses back across the placenta and is metabolized by the mother. There are also specific transport mechanisms in the placenta that actively transport specific nutrients. Calcium is such a nutrient; a 100 to 140 mg/kg/day accretion is required by the fetus in the third trimester (35). Lead is transported via the calcium transporter. Fetal blood lead concentration is equivalent to maternal blood lead concentration (36).

Percutaneous

Transdermal pathways of absorption are particularly important for lipophilic compounds. The skin undergoes enormous changes with each developmental stage, which alters the properties of absorption.

The dermis of a fetus is unkeratinized (37) and is thus without one of the major barriers of the skin. Although xenobiotics have been described in amniotic fluid (38), the transdermal absorption of these compounds has not been studied. Keratinization occurs over the initial 3 to 5 days

following birth and is independent of gestational age. Therefore, the skin of a newborn remains a particularly absorptive surface. Several epidemics have been described involving percutaneous absorption of xenobiotics, including hypothyroidism from iodine in betadine scrub solutions (39), neurotoxicity from hexachlorophene baths (40), and hyperbilirubinemia from a phenolic disinfectant (41). An additional factor in the absorption of these chemicals transdermally is the larger surface-to-volume ratio of newborns compared to older children and adults.

Respiratory Tract

During prenatal life, the fetus makes breathing motions. Although the net flux of fluid is from the lungs out of the trachea into the amniotic fluid, some xenobiotics in amniotic fluid may be in contact with the respiratory epithelium. Studies on this pathway are limited. It has been noted that maternal smoking during pregnancy is associated with significant reductions in forced expiratory flow rates (42).

The surface absorptive properties of the lung probably do not change during development. However, from birth to adolescence, the lung continues to develop alveoli (43). A consequence of this development is an increasing surface absorptive area in the lung.

Gastrointestinal Tract

The gastrointestinal (GI) tract undergoes numerous changes during development. The fetus actively swallows amniotic fluid (44). Xenobiotics are known to be present in amniotic fluid, but prenatal absorption from the GI tract has not been investigated.

Following delivery, the gastric pH is relatively high and does not achieve adult levels of acidity until several months of age (45). The difference in pH will markedly affect xenobiotic absorption from the stomach, as it will change the ionization status of these chemicals (46). In addition, under low levels of acidity, bacterial overgrowth in the small bowel and stomach may result. The absorption of nitrites formed by bacteria from ingestion of formula reconstituted with well water with nitrate contamination resulted in several cases of methemoglobinemia in Iowa (47).

The small bowel is felt to express specific transport mechanisms in the newborn. In the newborn mouse and rat, maternal IgM and IgG present in colostrum are specifically transported

across the small bowel and into the blood. Whether these mechanisms are present in humans has not been proved (48). The bowel also responds to increased nutritional needs by increasing absorption of the particular nutrient. For example, growing children require more calcium than adults for continued bone growth. Thus, they absorb more calcium from intraluminal contents than adults. However, they also absorb more lead from the GI tract than adults because of this enhanced absorption. It is estimated that an adult will absorb 10% of ingested lead, whereas a 1- to 2-year-old child will absorb 50% of ingested lead (49).

Distribution

The tissue distribution of chemicals varies with developmental stage of the child. For example, many drugs in the newborn have higher apparent volumes of distribution (50). In animal models, it has been shown that lead is retained to a larger degree in the infant animal brain than in the adult (51). Lead also accumulates more rapidly in children's bones, doubling between infancy and the late teen years (52).

Metabolism

Metabolism of chemicals may result in their activation or deactivation. These enzymes involved in the biotransformation of chemicals can be categorized into two groups, Phase I and Phase II enzymes. Phase I enzymes promote formation of a conjugable group, and phase II enzymes catalyze the conjugation of a more polar compound to the conjugable group such that the resulting conjugate is more polar and therefore more easily excreted. Not only does developmental stage determine the activity of these metabolic pathways, but also the genetic polymorphisms of each locus determine the activity of each component enzyme. The family of glutathione *S*-transferases, phase II enzymes, illustrates both of these points. The glutathione *S*-transferases (GST) are a large and complex family of enzymes which share the catalytic activity of glutathione conjugation to a second substrate with a conjugable group (53). They can be separated into four families of enzymes: α , μ , π , and microsomal. The μ family is lacking in 50% of individuals (54). Smokers with lung cancer have a higher incidence of lacking the μ glutathione transferases (55). Thus, these individuals have a genetic susceptibility to carcinogenesis from cigarette smoke. The expression of the families of GST show a

marked tissue specificity. GST π is only found in placenta (56,57); the Yc isozyme of GST α is not expressed in brain, but the Yb₃ isozyme of GST μ is only expressed in brain (58,59). Developmental regulation is evident in that 50% of GST activity in fetal liver is GST π , which is not expressed in adult liver (60).

Developmental regulation is more complex in the P450 cytochrome family. [Nebert and Gonzales (61) present a complete review.] Clinically this is important for the pediatrician to know in order to prescribe medications accurately. Theophylline is metabolized by the P450 cytochrome system. Initially, during the newborn period, the half-life of theophylline is prolonged, requiring dosing twice a day. However, P450 cytochrome expression increases over the first few months of life, decreasing drug half-life and necessitating more frequent dosing. If one examines urinary metabolites of theophylline during this period, one sees a difference in the pattern of metabolites denoting complex developmental stages in the expression and activity of the P450 cytochromes (61). The half-life of theophylline is again prolonged during adolescence, possibly as a consequence of competition with steroid hormones (62). Dosing interval must again be prolonged to avoid toxicity.

Another clinical example of developmental changes in metabolism is the case of acetaminophen. In the adult, as well as the pregnant adult, high levels of acetaminophen may cause fatal hepatotoxicity. However, infants delivered to mothers with high acetaminophen levels will also have elevated acetaminophen levels in blood, but will not sustain liver damage. It is thought that the lack of the fetus's ability to metabolize the acetaminophen protects the fetus from end-organ damage (63,64).

From these two examples, one can conclude that biotransformation of xenobiotics is developmentally regulated and may either protect or harm the individual.

Excretion

Kidney function is also developmentally regulated. At birth, glomerular filtration rate is a fraction of normal adult values. It gradually increases to adult values by approximately 1 year of age. The ability to concentrate urine is also developmentally regulated, the newborn being relatively poor at concentrating urine. By 16 months of age, renal function has reached adult capabilities (65).

Target Organ Susceptibility

Children are also different than adults because their organs are undergoing growth and differentiation. Both of these processes may be affected by xenobiotics. The result of exposure to xenobiotics may be different in children than adults, both in the degree of severity of effect and also in the nature of the effect. Since children's bodies are growing and developing, these processes may be disrupted as a result of environmental exposures, leading to different outcomes. Examples of such outcomes are prenatal and postnatal growth retardation, diminished IQ, precocious puberty, microcephaly, and diminished lung volume.

Growth occurs by three mechanisms: auxelic, where growth occurs by cells becoming larger; multiplicative, where growth occurs by cells dividing; and accretionary, where ground substance and non-living structural components accumulate (66). Multiplicative growth is felt to be complete at 6 months of gestation for those tissues not undergoing continual turnover such as epithelial cells. All subsequent growth is accretionary or auxelic. Cells undergo two further processes to become the adult organism, differentiation and migration. Differentiation is the process by which cells take on their particular chemical operations and lose the ability to divide. These events may be triggered by hormone-receptor interactions. Some environmental agents may mimic hormones and alter the differentiation of some tissues. Chlorinated insecticides are an example of this mechanism. Recent studies have shown effects on the reproductive system from exposure to chlordane (67).

Cell migration is necessary for certain cells to reach their destination for function. Neurons, for example, originate in the germinal matrix, then migrate out along radial glia to a predestined location in one of the many layers of the brain (68). Xenobiotics may have a profound effect on this process, as shown in children with fetal alcohol syndrome. Prenatal exposure to ethanol may result in interruption in this process severe enough to cause lissencephaly (69).

Examples of organs that have a prolonged period of postnatal development are the brain and the lungs. Myelination of the brain is not complete until adolescence (70). Alveolarization is not complete until adolescence (43). This protracted period of growth and development increases the vulnerability of these organs. For example, intracranial tumors are frequently treated by radiation therapy in adults, with uncomfortable but reversible side effects (71). However, in infants, radiation therapy is avoided because of the profound and permanent effects on the developing central nervous system.

Another example of the unique vulnerability of children is the neurotoxic effects of lead. The current blood lead concentration of concern for children is 10 µg/dl (72). This level is based on studies by numerous investigators (73) that show that children with blood lead concentrations greater than 10 µg/dl have measurable decreases in intelligence quotient. The occupational limit for adults is 60 µg/dl, at which no encephalopathy is noted, but may impair kidney function, fertility, and peripheral nerves (49).

That the developing lung may also be compromised by exposure to environmental agents is illustrated by studies of the effects of environmental tobacco smoke on children. It has been shown that the FEV₁'s of children exposed to environmental tobacco smoke (ETS) are measurably slower than children with no exposure (74).

Tissues undergoing proliferation and terminal differentiation are particularly susceptible to carcinogenesis (75). This increased susceptibility is due to the shortened time period for DNA repair and the multiple changes that are occurring within the DNA, such as interaction with growth factors, the switching on of genes as well as the switching off of genes. All are likely sites for interaction with chemicals that will interrupt the sequence of events. A clinical example is the epidemic of scrotal cancer among the pubertal chimney sweeps of Victorian England (76). Chimney sweeps were usually adolescents with

developing secondary sexual characteristics. Occupational exposure to carcinogens such as soot was common, but the site of the tumor is uncommon outside this situation. Thus, it can be hypothesized that the scrotum, while undergoing terminal differentiation, had increased susceptibility to the carcinogen.

Summary

This presentation has attempted to outline the reasons why children cannot be considered little adults in the area of environmental medicine. Their exposures are different, their pathways of absorption are different, their tissue distribution is different, their ability to biotransform and eliminate chemicals is different, and their bodies respond differently to environmental chemicals and radiation. Each of these differences is dependent on the developmental stage of the child—all children are not the same! Each of these differences must be taken into account when considering the health impacts of a particular exposure on the population. Our database is still incomplete as regards pediatric environmental medicine.

What can the practitioner do? The roles of educator, investigator, and advocate are extremely important when assessing children for their environmental health. Prevention is the most important intervention in this field. Parents, children, teachers, community leaders, and policy makers need to be educated about the unique vulnerability of children to environmental pollution. Most environmentally caused diseases have been diagnosed by an alert clinician. Publication of case studies has allowed further description of environmentally mediated diseases. Finally, clinicians must be advocates for their patients. Most regulatory policies do not take the unique vulnerability of children into account when setting limits. A clinician must understand the basis for this unique vulnerability and all the factors that influence it to be an effective advocate.

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